PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/50, 9/00, 9/10

A1

(11) International Publication Number: WO 92/00731

(43) International Publication Date: 23 January 1992 (23.01.92)

(21) International Application Number: PCT/EP91/01268

(22) International Filing Date: 4 July 1991 (04.07.91)

(30) Priority data:
20908/A90 11 July 1990 (11.07.90) IT

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(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), SU, US.

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITION FOR RAPID SUSPENSION IN WATER

(57) Abstract

The invention provides a solid pharmaceutical composition for addition to water to produce a suspension of a drug comprising (a) a drug which is substantially water-insoluble or microencapsulated; (b) a thickening or suspending agent; (c) a pharmaceutically acceptable acid; (d) a pharmaceutically acceptable carbonate or bicarbonate; characterised in that the weight ratio of c + d:b is from 1:1.5 to 1:15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent (b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds. A method for preparing the composition is also described.

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PHARMACEUTICAL COMPOSITION FOR RAPID SUSPENSION IN WATER

The present invention relates to a pharmaceutical formulation suitable for the administration of drugs and in particular of microcapsules of drugs in a monodose sachet form, the contents of which are poured into water at the moment of use. A process for preparing the formulation is also included.

In the description and the claims which follow we will use mostly the terms microcapsules or microencapsulated drugs, but the present invention can also be applied to solid drug particles (powders, crystals, granules) which are insoluble or slightly soluble in water or drinkable aqueous liquids (milk, fruit juices, etc.) and of which one desires to obtain an extemporary and homogeneous suspension.

In the following description and claims the term:
- "microcapsule" is used to indicate drug particles, powders, crystals, granules, pellets and also liquid drops, coated in a polymeric membrane
- "microencapsulation" is generically the process used for the application of a membrane
- "packet or monodose sachet" is a container which contains a single dose of drug plus the excipients of the formulation
- "thickening or suspending substances" are substances which dissolve in water and which increase in density and viscosity allowing solid particles to be suspended.

Microencapsulation is a process known from some time and consists of coating substances with a continuous film based on natural or synthetic polymers.

drug into a more easily used form, such as for example, converting it from a liquid state into a powder composed of microcapsules.

A common form of dosage for the oral administration of drugs, and especially of microencapsulated drugs, is that of monodose sachets. This moveover is the most convenient solution, if not the only one, if one must administer high doses of drugs. Monodose sachets containing mircocapsules have been prepared in the past, sometimes also on an industrial scale, as cited in the volume "Microencapsulation" by J.R. Nixon, Chapter 7, page 93.

However they often present various disadvantages due especially to the hydrorepulsion of polymers making up the microcapsule membrane (for example polymers with a base of cellulose or waxy substances) and to the specific weight of the microencapsulated substances and therefore of the said microcapsules.

In fact when the contents of the sachets were poured out, as usual, in a glass of water or in fruit juice or in milk, the microcapsules formed a sediment on the bottom of the glass or floated on the surface, adhering partly to the walls of the said glass. This brought a notable inaccuracy to the quantity of the drug taken as well as poor acceptance by the patient who saw the particles floating or felt an unpleasant scraping sensation in the mouth or throat when swallowing the contents at the bottom of the glass where the mass of sedimented particles was found.

The addition of thickening substances could delay and

after 20-30 seconds at the most. After this time the thickener is still not sufficiently dissolved and so a homogeneous suspension is not obtained and the previously cited difficulties are only partially eliminated.

It is therefore considered necessary to find a system which reduces the mixing times. During the research carried out on this matter, most surprisingly it was found that if an acid and a base substance are added, the thickening of the liquid and the homogeneous suspension of the microcapsules is generally obtained by mixing for only 15-20 seconds.

According to the present invention there is provided a solid pharmaceutical composition for addition to water to produce a suspension of a drug comprising

a) a drug which is substantially water-insoluble or microencapsulated;

b) a thickening or suspending agent;

c) a pharmaceutically acceptable acid;

d) a pharmaceutically acceptable carbonate or bicarbonate; characterised in that the weight ratio of c + d : b is from 1 : 1.5 to 1 : 15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.

It is necessary however that the acid and base

granulometry as the thickener and suspending them together with this;
-in a quantity so as not to allow effervescence but sufficient to obtaining the desired effect;
-in a suitable ratio with respect to each other and with the thickener.

As already cited the microcapsules can be prepared with various systems provided that the membrane which coats the drug to be constituted by a suitable polymer for pharmaceutical use.

The microcapsules will usually be comprised in weight of 3% to 50% polymer and from 50% to 97% drug. The polymer constituting the membrane must be permeable or soluble in the gastrointestinal juices in order to allow the release of the drug and its absorption.

The preferred polymer used is ethylcellulose, but as an illustrative and not limiting example polymers can also be cited such as for example polyacrylates, polymethacrylates, polyvinylchloride, polyvinylalcohol, polyethylene, polyamides, polysiloxanes, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose acetate succinate, cellulose acetate trimellitate, copolymers of maleic acid, derivatives of phthalic acid, and also polymers of natural origin such as gelatine, arabic gum and Shellac.

With regard to the drugs contained in the microcapsules, any pharmacologically active substance whether in a liquid or powdery form, crystalline or granular form can be coated with polymeric membrane

pharmaceutical composition as described above comprising mixing b) a thickening or suspending agent c) a pharmaceutically acceptable acid, d) a pharmaceutically acceptable base selected from carbonates and bicarbonates and a) a water insoluble or microencapsulated drug wherein the ratio of c + d : b is from 1 : 1.5 to 1:15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.

The preferred process consists substantially of the following operations:

1) Micronise, grind or anyway use the thickening substances with a granulometry less than 150 µm or better 75 µm;
2) micronise, grind or anyway use an acid or base substance, not soluble in the solvent with the same granulometry as the thickening substance;
3) suspend the thickening substance, in fine powder, in a solvent containing a binder; the thickener must be insoluble or at least only slightly soluble in the solvent in which the binding substance is dissolved; this, in turn, as well as obviously being soluble in the solvent, must also be soluble in water in order to "bind" the particles of the thickener to the support, but also to liberate them rapidly once in contact with the water;
4) suspend or dissolve the base and acid substances, in the suspension cited in the previous point;
5) apply the suspension thus obtained to granules

Corporation). As binders the following are cited as illustrative but not limiting examples; methylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxy-propylcellulose, hydroxybutylcellulose, polyethyleneglycols, polyvinylalcohols, polyvinylpyrrolidone, gelatine, starches, modified starches, arabic gum.

As the inert excipients, to which the suspension containing the thickener can be applied, the following are cited as an illustrative but not limiting example, sucrose, lactose, fructose, mannitol, anhydrous sorbitol, maltodextrine, glycine, alanine, pentaerythrite.

As the acid substances, the following are cited as an illustrative but not limiting examples: tartaric acid, citric acid, maleic acid, ascorbic acid, fumaric acid.

As the base substances, the following are cited as an illustrative but not limiting example: sodium bicarbonate, potassium bicarbonate, sodium carbonate and other water soluble carbonic acid salts.

To facilitate the water penetration one can also add a surfactant; cited as an illustrative but not limiting example are: sodium dioctylsulfosuccinate, sodium laurylsulphate, various esters of sorbitol and sorbitans with fatty acids etc.

The surfactant can be added in any phase of the operation, even if it is preferable to add it in phase 3) of the above described process, or mix it in a micronized form with the other solid excipients.

obtained.

Apply this suspension to the surfaces of the sorbitol granules having a granulometry less than 700µm.

To carry out this operation the suspension is poured on 2616g of sorbitol granules placed in a counter-rotating horizontal ball mixer.

Dry the granulate for 14 hours at about 40°C in a ventilation cupboard and sieve through a 700µm mesh.

B) Preparation of the Monodose Sachets.

In a cube mixer, homogeneously mix 2000g of the granules obtained in a) with 912g of granulated sorbitol and 88.2g of microcapsules of ambroxol HCl having an ethylcellulose membrane and titre of 850mg/g.

Divide the mixture in monodose sachets of paper/aluminium/heat sealed polythene.

3000mg of mixture contain 75mg of ambroxol HCl.

C) The content of a sachet is poured in half a glass of water (about 50ml) and stirred with a teaspoon for about 15 seconds obtaining a homogeneous suspension suitable for taking.

EXAMPLE 2

A) Preparation of the suspended granules.

In a 2 litre beaker, place 1600ml of 95% ethyl alcohol.

Add 72g of polyvinylpyrrolidone K30, 4.5g of acid saccharin, 77.7g of tartaric acid and stir until completely in solution.

Add, still stirring, 55g of ground potassium bicarbonate (granulometry less than 50 µm) and 1452g of guar gum (granulometry less than 50 µm).

alcohol.

Add 120g of polyvinylpyrrolidone K30, 72g of anhydrous citric acid and stir until a complete solution is obtained.

Add, still stirring, 48g of ground sodium bicarbonate (granulometry less than 100µm) and 1200g of xanthan gum (granulometry less than 100 µm).

Stir until a homogeneous suspension is obtained.

Apply this suspension to the surfaces of the sucrose granules having a granulometry between 210-700µm.

To carry out this operation the suspension was sprayed on 8140g of sucrose granules put in a flat-bottomed laboratory coating pan.

Dry the granulate in said coating pan and sieve through a 850µm.

B) Preparation of monodose sachets.

In a cube mixer, place 2000g of granules obtained in A), 620g of granulated sucrose, 880g of microcapsule potassium chloride (titre 860mg/g, ethylcellulose membrane, P.R. 8:1) 0.5g of talc, 1.5g of cherry flavouring.

Divide the mixture into monodose sachets made of paper/aluminium/thermosealed polythene.

3500mg of mixture contain 750mg of potassium chloride.

C) The contents of a sachet were poured into half a glass of water (about 50ml) and stirred with a teaspoon for about 15 seconds obtaining a homogeneous suspension suitable to be taken.

EXAMPLE 5

To check the advantage of the method described in this invention with respect to the granules which are object of the Italian patent no 1183574, a granular suspension was prepared using the same method and the same excipients cited in example 3 in point A) but without citric acid and without sodium bicarbonate.

The monodose sachets were prepared using the same method and the same composition described in example 3 in point B).

The contents of these sachets were poured into the same quantity of water described in example 3 in point C) and mixed with a spoon: to obtain a homogeneous suspension it is necessary to mix for 55-75 seconds, that is a 3-4 times longer than that in example 3.

EXAMPLE 6

To check the advantage of the method described in this invention with respect to the monodose sachets prepared according to the usual methods, the excipients sachets prepared according to the usual methods, the excipients described in example 3, point A) i.e. 260g of citric acid, 340g of sodium bicarbonate and 1090g of xanthan gum, are granulated with 170g of polyvinyl-pyrrolidone in an alcoholic solution in order to obtain granules smaller than 700 µm.

This granulate was mixed with 8140g of sucrose having a

CLAIMS

1. A solid pharmaceutical composition for addition to water to produce a suspension of a drug comprising

a) a drug which is substantially water-insoluble or microencapsulated;

b) a thickening or suspending agent;

c) a pharmaceutically acceptable acid;

d) a pharmaceutically acceptable carbonate or bicarbonate; characterised in that the weight ratio of c + d : b is from 1 : 1.5 to 1 : 15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.

2. A composition as claimed in Claim 1, wherein the weight ratio of c + d : b is from 1 : 1.5 to 1 : 5.

3. A composition as claimed in Claim 1 or Claim 2, wherein the weight ratio of c : d is from 1 : 0.5 to 1 : 1.5.

4. A composition as claimed in Claim 1, 2 or 3 wherein the acid is selected from tartaric, citric, pyruvic, malic, ascorbic and fumaric acids.

5. A composition as claimed in any one of Claims 1 - 4, wherein the carbonate or bicarbonate b) is selected from sodium bicarbonate, potassium bicarbonate, sodium carbonate and other water soluble carbonic acid salts.

12. Sachets containing unit doses of a composition as claimed in any one of the preceding Claims.

13. A method for preparing a pharmaceutical composition as claimed in any one of the preceding Claims 1 - 12 which method comprises mixing b) a thickening or suspending agent c) a pharmaceutically acceptable base selected from carbonates and bicarbonates and a) a water insoluble or microencapsulated drug wherein the ratio of c + d : b is from 1 : 1.5 to 1:15 and the amount of c + d is sufficient to obtain rapid hydration of the thickening or suspending agent b) when the composition is mixed with water such that a homogeneous suspension of the drug is obtained within 30 seconds.

14. A method as claimed in Claim 13, wherein the thickening or suspending agent b) has the same granulometry as the acid c) and base d).

15. A method as claimed in Claim 13 or 14, wherein the ingredients b, c and d are mixed in a non-aqueous solvent, then applied to a water soluble excipient and the mixture dried and then mixed with the drug.

16. A method as claimed in Claim 14, wherein the granulometry is less than 150 µm.

17. A method as claimed in any one of Claims 13 to 16, wherein the ingredients b, c and d are mixed to form a homogeneous suspension in a non-aqueous solvent in which a binder is dissolved and in which the ingredient b is substantially insoluble, the suspension is applied to a water soluble excipient and dried, then

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01268

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/50 ; A61K9/00 ; A61K9/10

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,2 125 577 (AKIYOSHI MATSUMAE) September 10, 1936 see page 1, column 1, line 1 - page 1, column 1, line 9 see page 1, column 2, line 10 - page 1, column 2, line 37 see page 2, column 1, line 3 - page 2, column 1, line 12 see claims 1-4	1-6

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[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 SEPTEMBER 1991	- 1. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BOULOIS D.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9101268
SA 48877

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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17/09/91

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-2125577		None		
WO-A-8606626	20-11-86	AU-B-	589644	19-10-89
		CA-A-	1274144	18-09-90
		EP-A,B	0222856	27-05-87
		JP-T-	62502859	12-11-87
		US-A-	5008117	16-04-91
US-A-3928252	23-12-75	None		
WO-A-8602834	22-05-86	DE-A-	3440288	07-05-86
		AU-B-	576399	25-08-88
		AU-A-	4931885	15-05-86
		AU-B-	584154	18-05-89
		AU-A-	5199086	03-06-86
		CA-A-	1254143	16-05-89
		EP-A,B	0181564	21-05-86
		EP-A,B	0232277	19-08-87
		JP-A-	61115023	02-06-86
		JP-T-	62501210	14-05-87
		US-A-	4762702	09-08-88
		US-A-	4888177	19-12-89